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Banting lecture 1990. Beta-cells in type II diabetes mellitus.

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In 1960, immunoassays of insulin first demonstrated significant quantities of circulating hormone in non-insulin-dependent (type II) diabetes and for 30 yr have fostered debate as to whether a beta-cell abnormality plays an etiological role in this syndrome. Early efforts to determine the adequacy of islet beta-cell function showed that obesity and its associated insulin resistance were major confounding variables. Subsequently, it was recognized that glucose not only directly regulated insulin synthesis and secretion but moderated all other islet signals, including other substrates, hormones, and neural factors. When both obesity and glucose are taken into account, it becomes clear that patients with fasting hyperglycemia all have abnormal islet function. Type II diabetes is characterized by a defect in first-phase or acute glucose-induced insulin secretion and a deficiency in the ability of glucose to potentiate other islet nonglucose beta-cell secretagogues. The resulting hyperglycemia compensates for the defective glucose potentiation and maintains nearly normal basal insulin levels and insulin responses to nonglucose secretagogues but does not correct the defect in first-phase glucose-induced insulin release. Before the development of fasting hyperglycemia, only first-phase glucose-induced insulin secretion is obviously defective. This is because progressive islet failure is matched by rising glucose levels to maintain basal and second-phase insulin output. The relationship between islet function and fasting plasma glucose is steeply curvilinear, so that there is a 75% loss of beta-cell function by the time the diagnostic level of 140 mg/dl is exceeded. This new steady state is characterized by glucose overproduction and inefficient utilization. Insulin resistance is also present in most patients and contributes to the hyperglycemia by augmenting the glucose levels needed for compensation. Decompensation and absolute hypoinsulinemia occur when the renal threshold for glucose is exceeded and prevents further elevation of circulating glucose. The etiology of the islet beta-cell lesion is not

known, but a hypothesis based on basal hyperproinsulinemia and islet amyloid deposits in the pancreas of type II diabetes is reviewed. The recent discovery of the islet amyloid polypeptide (IAPP) or amylin, which is the major constituent of islet amyloid deposits, is integrated into this hypothesis. It is suggested that pro-IAPP and proinsulin processing and mature peptide secretion normally occur together and that abnormal processing, secondary to or in conjunction with defects in hormone secretion, lead to progressive accumulation of intracellular IAPP and pro-IAPP, which in cats, monkeys, and humans form intracellular fibrils and amyloid deposits with a loss of beta-cell mass.(ABSTRACT TRUNCATED AT 400 WORDS)

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